

## REMARKS

Applicant's attorney wishes to thank the Examiner for the careful consideration given to the present application. Currently, claims 1-4, 8 and 10-28 are pending, claims 10-27 have been withdrawn and claims 5-7 and 9 have been cancelled. In the Advisory Action dated September 19, 2008, the Examiner stated that the Response to Final Office Action dated August 20, 2008 would not be entered because it purportedly failed to place the application in better form for appeal or in condition for allowance. While Applicant respectfully disagrees, Applicant submits the present Response and Amendment and Request for Continued Examination, which addresses each of the rejections set forth in the Final Office Action in the order presented therein.

### 35 U.S.C. § 103

Claims 1-2, 4 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Powis et al., *Anti-Cancer Drugs* 1996, 7(3), pages 121-126 (hereinafter referred to as "Powis") in view of Halperin et al, U.S. Patent No. 5,633,274 (hereinafter referred to as "Halperin"). Applicant respectfully disagrees.

It is respectfully submitted that Powis in view of Halperin fails to render claims 1-2 and 4-8 directed to a sustained release delivery composition comprising 1-methylpropyl 2-imidazolyl disulfide and a matrix including at least one polymer obvious because neither reference alone or in combination provides any evidence that a composition comprising 1-methylpropyl 2-imidazolyl disulfide and a matrix including at least one polymer could be formulated to provide the sustained release delivery of 1-methylpropyl 2-imidazolyl disulfide. The references fail to even disclose or suggest a sustained release composition of an 1-methylpropyl 2-imidazolyl disulfide. As set forth in *KSR Int'l Co. v. Teleflex Inc.*, "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable results*." 127 S. Ct. 1727, 1731 (U.S. 2007) (emphasis added). As acknowledged in the present Office Action, the nature of the art of pharmaceuticals and their delivery is highly *unpredictable*. The Office has provided no evidence that one ordinarily skilled in the art would recognize that the sustained release delivery systems disclosed in Halperin for imidazoles would be suitable for 1-methylpropyl 2-imidazolyl disulfide. There is no structural relationship between the imidazoles of Halperin and 1-methylpropyl 2-imidazolyl of the present claims. Notably, Halperin fails to even disclose an example of an imidazole in a

sustained release delivery system, and obviously fails to disclose an example of an imidazole in a sustained release delivery system that contains a polymer matrix. Accordingly without a specific teaching that asymmetric disulfides, and particularly 1-methylpropyl 2-imidazolyl disulfide, could be formulated into a sustained release delivery composition, there is no reasonable expectation of success in view of the highly unpredictable nature of the art.

Additionally, as expressly set forth in the specification, the sustained delivery of 1-methylpropyl 2-imidazolyl disulfide resulted in an unexpectedly increased and prolonged decrease in thioredoxin levels. Specifically, Applicant has provided evidence comparing the level and length of inhibition of thioredoxin levels following (i) a 1 hour infusion of 1-methylpropyl 2-imidazolyl disulfide (also referred to as PX-12) and (ii) a sustained 3 hour infusion of 1-methylpropyl 2-imidazolyl disulfide of identical dosages. Figure 2 depicts the plasma thioredoxin levels prior to and following a 72 mg/m<sup>2</sup> (●) and 96 mg/m<sup>2</sup> (▲) dose of 1-methylpropyl 2 imidazolyl disulfide that was administered over a 1 hour period. Figure 3 depicts the plasma thioredoxin levels prior to and following a 72 mg/m<sup>2</sup> (●) and 96 mg/m<sup>2</sup> (▲) of 1-methylpropyl 2 imidazolyl disulfide that was administered over a 3 hour period. When administered over a 3 hour period, the same dose of 1-methylpropyl 2 imidazolyl disulfide resulted in a greater decrease in plasma thioredoxin levels in the patients and also maintained the decrease in plasma thioredoxin levels for a longer period of time. Also as shown in Figure 9, when the infusion length was increased to 3 hours (top line; black circle) from 1 hour (bottom line; red circle) for a dose of 72 mg/m<sup>2</sup> (●) of 1-methylpropyl 2 imidazolyl disulfide, the thioredoxin levels were constantly decreased at significantly lower levels and these decreased thioredoxin levels were consistently maintained for a significantly longer period of time. It would not be expected, and in fact is unexpected and surprising that by increasing the administration time of a drug, and in particular 1-methylpropyl 2 imidazolyl disulfide, (*without* increasing the total dosage of such drug), would result in greater inhibition of plasma thioredoxin levels. Such greater than expected results are evidence of the nonobviousness of the present claims. See MPEP 716.02(a). While Applicant can provide an affidavit to further explain and evidence such nonobviousness, it is respectfully submitted that the specification provides more than sufficient evidence of nonobviousness and may be relied upon without the need of a declaration. See MPEP 716.02(b). In addition, it is respectfully submitted that the sustained delivery of 1-methylpropyl 2-imidazolyl disulfide resulted in an unexpected improvement of

adverse aspects, particularly a malodor, that were observed in clinical trials during the administration a non-sustained delivery of 1-methylpropyl 2-imidazolyl disulfide to patients.

In the Advisory Action, the Examiner takes the position that the unexpected results are not commensurate in scope with the instant claims, specifically asserting that the results merely demonstrate the decrease of thioredoxin employing the sustained 3 hour infusion of 1-methylpropyl 2-imidazolyl disulfide, and further it is not clear which polymer was employed. As noted above, the unexpected nature of the results speak for themselves; that is, by sustaining the delivery of the same dose 1-methylpropyl 2-imidazolyl disulfide over a three-hour period from a 1 hour period, both the extent and duration of thioredoxin inhibition is significantly increased (even though the total amount of drug delivered is identical). It is respectfully submitted that the sustained delivery of the 1-methylpropyl 2-imidazolyl disulfide, which may be accomplished by, e.g., the inclusion of a polymer in the pharmaceutical composition, is a patentable aspect of the presently claimed invention. The claims are directed to “a composition for sustained release delivery” and the specification discloses that sustained delivery or release can be accomplished by a composition that is capable of releasing an asymmetric disulfide to the body for a prolonged period of time, e.g., for at least about 3 hours...” See paragraph [0071] of the specification. The specification teaches on skilled in the art how to make and use such a composition, including the use of polymers in the composition to arrive at a pharmaceutical composition for sustained release delivery as described in the specification (see, e.g., paragraphs [0071]-[0095]. Accordingly, for the foregoing reasons, this rejection should be withdrawn.

Claims 1-2, 4 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Oblong et al., Cancer Chemother. Pharmacol. 1994, 34: 434-438 (hereinafter referred to as “Oblong”) in view of Halperin. Applicant respectfully disagrees. Oblong does not speak to the suitability of 1-methylpropyl 2-imidazolyl disulfide as a potential therapeutic agent, and certainly fails to disclose anything regarding the suitability of delivering 1-methylpropyl 2-imidazolyl disulfide over at least a 3 hour period. It is respectfully submitted that for the reasons set forth above, namely the unpredictable nature of the present claims and the unexpected results specifically disclosed by Applicant, claims 1-2 4 and 8 are not obvious over Oblong in view of Halperin and this rejection should be withdrawn.

Claims 3 and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Powis or Oblong in view of Royer, U.S. Patent No. 5,783,214 (hereinafter referred to as "Royer"). Applicant respectfully disagrees.

It is respectfully submitted that Powis or Oblong in view of Royer fails to render claim 3 directed to a sustained release delivery composition comprising 1-methylpropyl 2-imidazolyl disulfide and a matrix including at least one hydrophilic polymer obvious because neither reference alone or in combination provides any evidence that a composition comprising 1-methylpropyl 2-imidazolyl disulfide and a matrix including at least one hydrophilic polymer could be formulated to provide the sustained release delivery of 1-methylpropyl 2-imidazolyl disulfide. The references fail to even disclose or suggest a sustained release composition of 1-methylpropyl 2-imidazolyl disulfide with a hydrophilic polymer. As set forth in *KSR Int'l Co. v. Teleflex Inc.*, "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable results*." 127 S. Ct. 1727, 1731 (U.S. 2007) (emphasis added). As acknowledged in the present Office Action, the nature of the art of pharmaceuticals and their delivery is highly *unpredictable*. Further, as noted by Royer, delivery systems of medicinal agents is a challenge because, among other things, the medicinal may be chemically modified during formulation. The delivery systems of Royer are specifically designed for the delivery of proteins, and there is no teaching or suggestion that the delivery of proteins using the systems of Royer could be applied to 1-methylpropyl 2-imidazolyl disulfide. The Office has provided no evidence that one ordinarily skilled in the art would recognize that the sustained release delivery systems disclosed in Royer for proteins would be suitable for asymmetric disulfides disclosed in Powis and Oblong. There is no structural relationship between the proteins of Royer and 1-methylpropyl 2-imidazolyl disulfide of the present claims and the disclosure of "anticancer drugs" in Royer is a genus of compounds that have no structural relationship and merely provide a functional property. Accordingly without a specific teaching that 1-methylpropyl 2-imidazolyl disulfide could be formulated into a sustained release delivery composition, there is no reasonable expectation of success in view of the highly unpredictable nature of the art.

Additionally, as set forth above, Applicant has provided more than sufficient evidence of the unexpected results of a sustained release delivery of 1-methylpropyl 2-imidazolyl

disulfide. Accordingly, claim 3 is not obvious over Powis or Oblong in view of Royer, and this rejection should be withdrawn.

Claims 1-2 and 4 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kirkpatrick et al. Eur. J. Med. Chem. 1992, 27, pages 33-37 (hereinafter referred to as “Kirkpatrick”) in view of Halperin. Applicant respectfully disagrees. It is respectfully submitted that for the reasons set forth above, namely the unpredictable nature of the present claims and the unexpected results specifically disclosed by Applicant, claims 1-2, 4-7 and 9 are not obvious over Kirkpatrick in view of Halperin and this rejection should be withdrawn.

#### Obviousness-Type Double Patenting

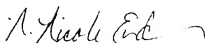
Claims 1-4, 8-9 and 28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 49, 52-60, 63-69 and 71 of co-pending U.S. Application No. 10/366,751. Claims 1-4, 8-9 and 28 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-10 of co-pending U.S. Application No. 10/600,957. Applicant respectfully disagrees. As set forth above, Applicant has shown unexpected results in inhibiting thioredoxin levels for the sustained delivery of 1-methylpropyl 2-imidazolyl disulfide in the specification, which evidences the nonobviousness of the current claims in light of the cited references. Notwithstanding, solely to expedite allowance of the present application, Applicant submits herewith a terminal disclaimer for each of the above-identified applications. Accordingly, this rejection should be withdrawn.

### CONCLUSION

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,



By: \_\_\_\_\_  
N. Nicole Endejann  
Reg. No. 50,229

Dated: October 20, 2008  
PEPPER HAMILTON LLP  
500 Grant Street  
One Mellon Bank Center, 50<sup>th</sup> Floor  
Pittsburgh, PA 15219  
(412) 454-5869  
(412) 281-0717 - facsimile